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(21) International Application Number: PCT/US93/10163 (22) International Filing Date: 22 October 1993 (22.10.93) (30) Priority data: 966,241 26 October 1992 (26.10.92) US (60) Parent Application or Grant (63) Related by Continuation US 966,241 (CON) Filed on 26 October 1992 (26.10.92) (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only) : NELSON, Edward, B. [US/US]; Three Wayne Circle, Lower Gwynedd, PA 19002 (US). SWEET, Charles, S. [US/US]; 1203 Meissen Court, Ambler, PA 19002 (US). (74) Agent: DANIEL, Mark, R.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: COMBINATIONS OF ANGIOTENSIN-II RECEPTOR ANTAGONISTS AND DIURETICS (57) Abstract Pharmaceutical formulations comprising as active ingredients an angiotensin-II receptor (A-II) antagonist at a dose level normally found effective as an antihypertensive and a diuretic at a dose level below its minimum effective dose, demonstrate greater efficacy than would be expected in returning the blood pressure of hypertensive patients to normotensive values.		

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TITLE OF THE INVENTIONCOMBINATIONS OF ANGIOTENSIN-II RECEPTOR
ANTAGONISTS AND DIURETICS5 BACKGROUND OF THE INVENTION

Both diuretics and A-II antagonists have an effect on the renin-angiotensin-aldosterone system. A-II antagonists lower blood pressure by blocking the angiotensin II receptors important in regulating blood pressure. Diuretics regulate the sodium-balance, and
10 thereby also extracellular fluid volume. The resultant decrease, both in sodium and fluid volume, following therapy with diuretics activates the renin-angiotensin-aldosterone system. This compensatory response will, to some degree, counteract the blood-pressure lowering effect of the diuretic. When a diuretic and an A-II antagonist are combined the
15 different pharmacological actions of these two drugs will, influence the effect of the other. There is accordingly a logical rationale for combining these two pharmacological agents.

It is possible to establish the highest non-pharmacological active dose of diuretic, i.e. a dose that is so low that it has essentially no
20 effect on blood pressure, and no apparent adverse effects. The clinically non-effective dose of diuretic, however, will still activate the renin-angiotensin-aldosterone system and although it has no effect on blood pressure, it will, nonetheless, have a potentiating effect on an A-II antagonist action in lowering blood pressure.

25 In a recently completed study of the effects of different doses of HCTZ on blood pressure and various metabolic parameters, doses ranging from 3 mg to 25 mg were investigated. 25 mg HCTZ produced significant effects on blood pressure and the metabolic parameters. 12.5 mg of HCTZ was at the threshold of an effective
30 antihypertensive response, and this dose also altered metabolic parameters. In contrast, HCTZ at 3 and 6 mg were not different from placebo in terms of blood pressure and metabolic end-points.

Based on this study it can be concluded that the 6 mg or 6.25 mg dose is close to the highest non-pharmacological dose of HCTZ.

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SUMMARY OF THE INVENTION

This invention is concerned with pharmaceutical formulations for the treatment of essential hypertension and disorders associated therewith such as heart failure, cardiac or vascular hypertrophy, renal failure, proteinuria, ischemia or restenosis, which have as active ingredients an A-II antagonist and a diuretic wherein the diuretic is at a dose level below the recognized clinically effective dose.

With these formulations the A-II antagonist is found to have greater efficacy in reducing elevated blood pressure to normal levels than it would have if used at the same dose as monotherapy. At the same time the diuretic is being administered at dose levels that would be ineffective as an antihypertensive if used alone and similarly ineffective in causing adverse reactions.

DETAILED DESCRIPTION OF THE INVENTION

The novel pharmaceutical formulations of this invention comprise: a pharmaceutical carrier; an A-II antagonist at the dose level normally employed in monotherapy, which is usually about 0.1 to about 1000 mg preferably about 1-100 mg, depending on the A-II antagonist; and a diuretic at a dose level which is the highest non-pharmacological dose.

The formulation is designed for oral administration and is presented as tablets, capsules, gel caps, caplets, sublingual dosage form or as a sustained release formulation. It may also be designed as an elixir for oral administration, a suppository for rectal administration, or a patch for transdermal administration, or a biodegradable stint for local intraarterial administration.

Illustrative of the excipients which can be incorporated in tablets, capsules and the like are: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring

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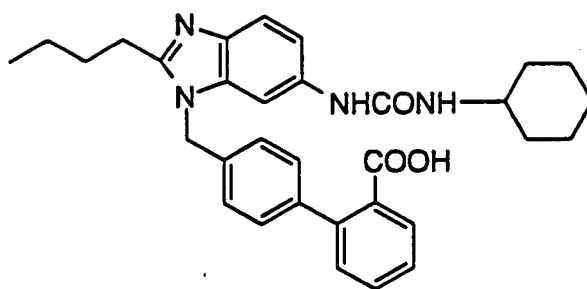
agent such as peppermint, oil of wintergreen or cherry. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

The novel formulations of this invention are useful in the treatment of essential hypertension, and heart failure, cardiac or vascular hypertrophy, renal failure, proteinuria, ischemia or restenosis.

Typical of the A-II antagonists useful in the novel formulation and method of treatment of this invention are the following compounds I through XI:

- 4 -

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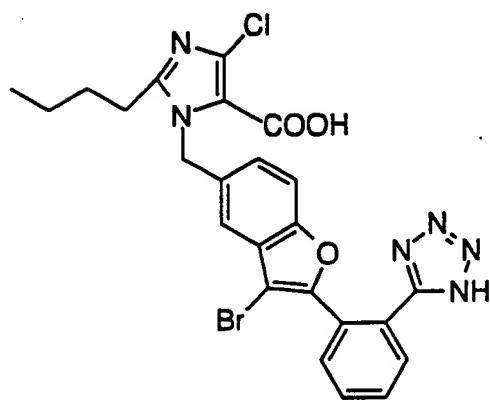


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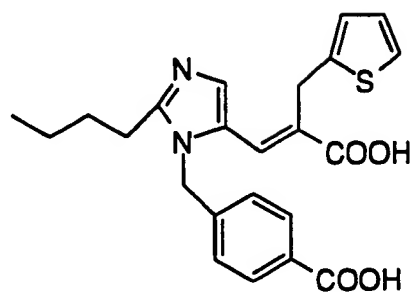
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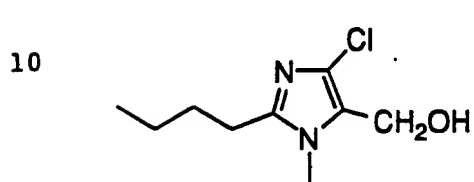
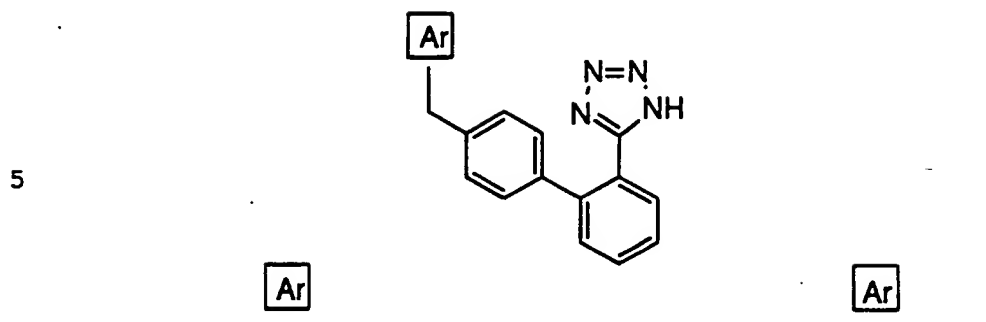
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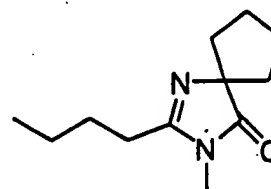


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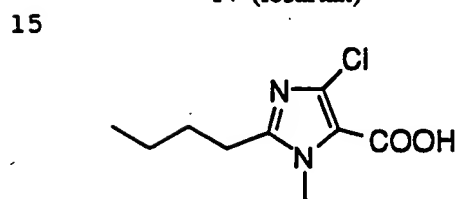
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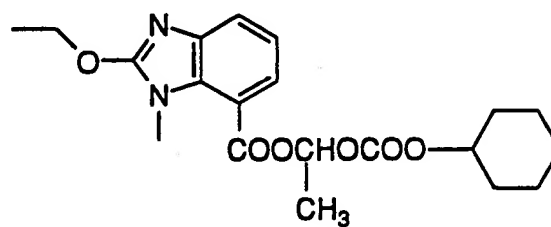
IV (losartan)



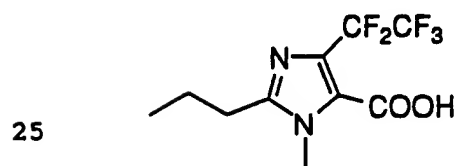
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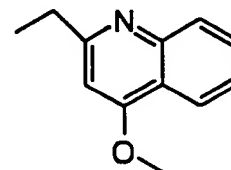
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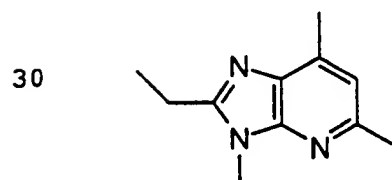
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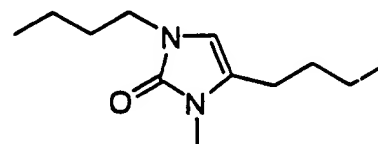
VI



X



VII



XI

- 6 -

The preferred A-II antagonist for use in the novel formulation and method of treatment of this invention is compound IV.

The diuretics useful in the novel formulation and method of treatment of this invention are: hydrochlorothiazide (HCTZ),
 5 furosemide, altizide, trichlormethazide, triflumethazide, bemetizide, cyclothiazide, methylclothiazide, azosemide, chlorothiazide, butizide, bendroflumethazide, cyclopenthiazide, benzclortriazide, polythiazide, hydroflumethazide, benzthiazide, ethiazide, penflutazide, chlorthalidone, butazolimide, spironolactone, amiloride or triamterene.

10 Preferred diuretics for incorporation in the novel formulation of this invention are hydrochlorothiazide, trichlormethazide, furosemide, chlorthalidone, and altizide, especially hydrochlorothiazide.

15 In the specification and claims hereof, the naming of an A-II antagonist or diuretic such as losartan or hydrochlorothiazide respectfully is meant to include salts thereof.

The novel method of treatment of this invention comprises the administration of a unit dose of the novel pharmaceutical
 20 formulation, one to three times a day depending on the patient and the severity of the indication being treated. Usually once or twice a day is adequate.

EXAMPLE 1

25	<u>Component</u>	<u>Amount (mg)</u>		
		<u>A</u>	<u>B</u>	<u>C</u>
	losartan (IV)	100	50	25
	hydrochlorothiazide	6.25	6.25	6.25
	sodium bicarbonate	10	5	2.5
30	lactose	154	164.1	198.1
	starch NF	22	22	22.77
	pregelatinized starch NF	2.2	2.2	5.06
	magnesium stearate	1.1	1.0	0.90

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The excipients shown in Example 1 are exemplary of the excipients used in each of the other examples that follow.

EXAMPLE 2

5

<u>Component</u>	<u>Amount (mg)</u>		
	<u>1</u>	<u>2</u>	<u>3</u>
Compound I	100	50	25
hydrochlorothiazide	6.25	6.25	6.25

10

EXAMPLE 3

15

<u>Component</u>	<u>Amount (mg)</u>		
	<u>1</u>	<u>2</u>	<u>3</u>
Compound II	100	50	25
hydrochlorothiazide	6.25	6.25	6.25

20

EXAMPLE 4

25

<u>Component</u>	<u>Amount (mg)</u>		
	<u>1</u>	<u>2</u>	<u>3</u>
Compound III	100	50	25
hydrochlorothiazide	6.25	6.25	6.25

EXAMPLE 5

30

<u>Component</u>	<u>Amount (mg)</u>		
	<u>1</u>	<u>2</u>	<u>3</u>
Compound V	100	50	25
hydrochlorothiazide	6.25	6.25	6.25

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EXAMPLE 6

5	<u>Component</u>	<u>Amount (mg)</u>		
		<u>1</u>	<u>2</u>	<u>3</u>
	Compound VI	100	50	25
	hydrochlorothiazide	6.25	6.25	6.25
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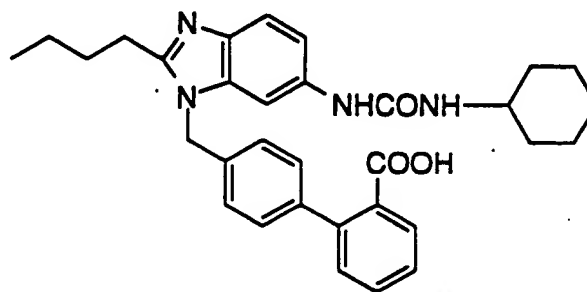
- 9 -

WHAT IS CLAIMED IS:

1. A pharmaceutical formulation comprising a pharmaceutical carrier; about 0.1-1000 mg of an A-II antagonist; and an effective non-pharmacological dose of a diuretic.

2. The pharmaceutical formulation of Claim 1, wherein the A-II antagonist is selected from

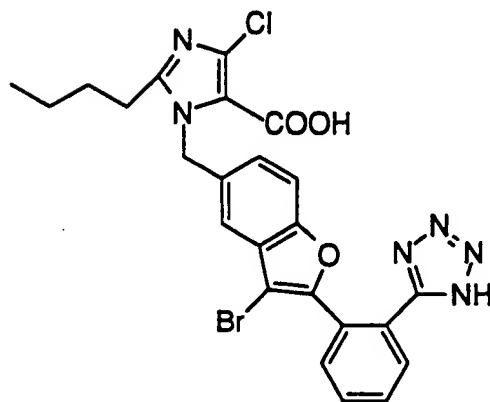
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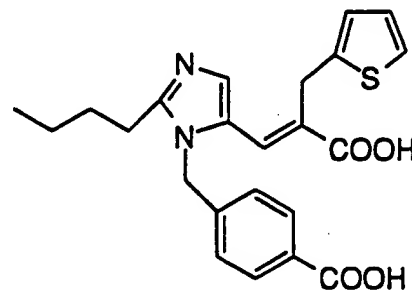
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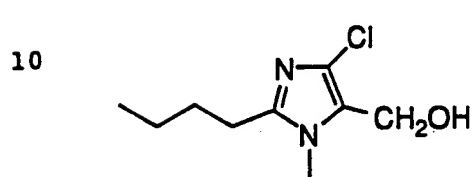
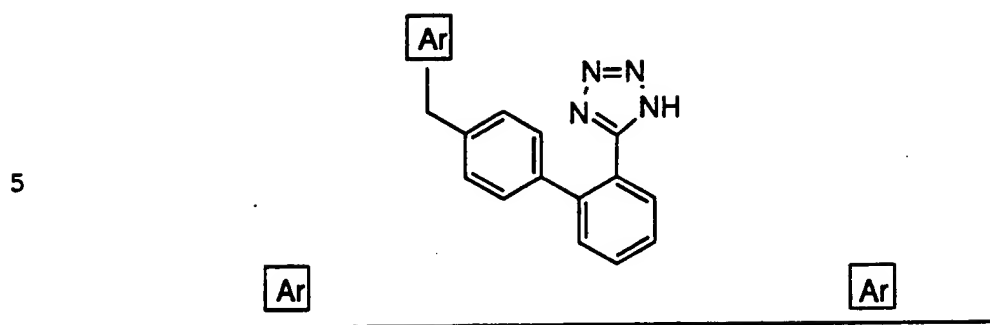
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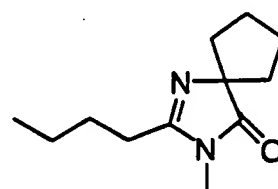


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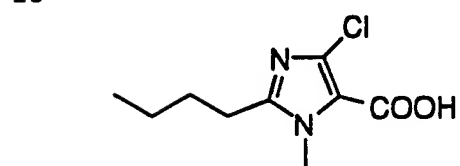
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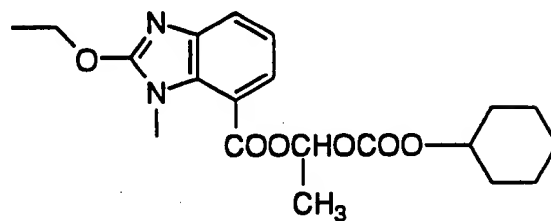
IV (losartan)



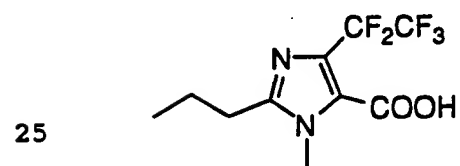
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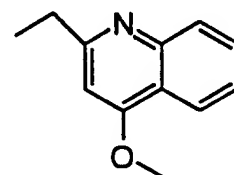
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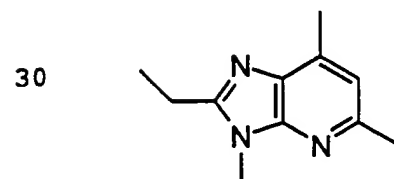
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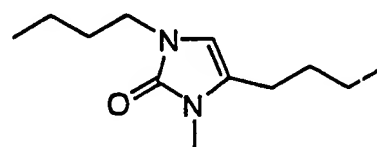
VI



X



VII



XI

- 11 -

and the diuretic is selected from hydrochlorothiazide (HCTZ), furosemide, altizide, trichlormethazide, triflumethazide, bemetizide, cyclothiazide, methylchlothiazide, azosemide, chlorothiazide, butizide, bendroflumethazide, cyclopenthiazide, benzclortriazide, polythiazide, hydroflumethazide, benzthiazide, ethiazide, penflutazide, chlorthalidone, butazolimide, spironolactone, amiloride or triamterene.

3. The formulation of Claim 2, wherein the A-II antagonist is losartan.

10

4. The formulation of Claim 3, wherein the the diuretic is hydrochlorothiazide.

5. The formulation of Claim 4 comprising 2.5, 5.0, 10, 12.5, 25, 50 or 100 mg of losartan and 6.25 mg of hydrochlorothiazide.

15

6. A method of treating hypertension and heart failure, which comprises the administration to a patient in need of such treatment of a pharmaceutical formulation comprising a pharmaceutical carrier; about 0.1-1000 mg of an A-II antagonist; and an effective non-pharmacological dose of a diuretic.

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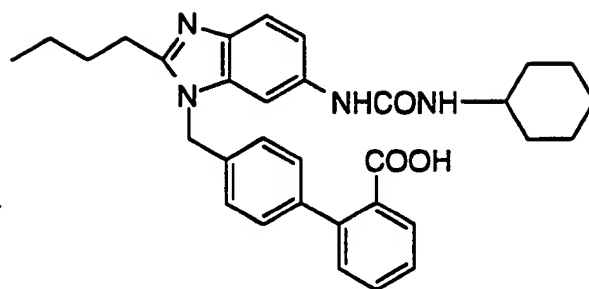
7. The method of Claim 6, wherein the A-II antagonist is selected from

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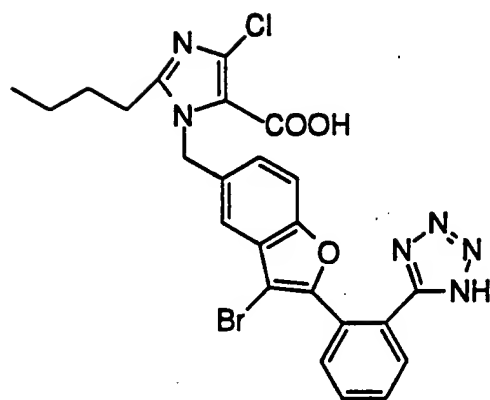


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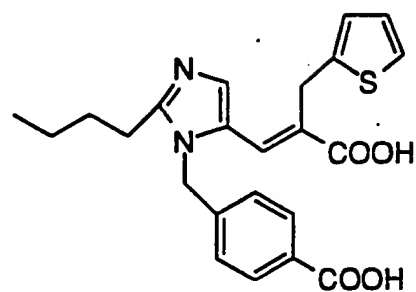
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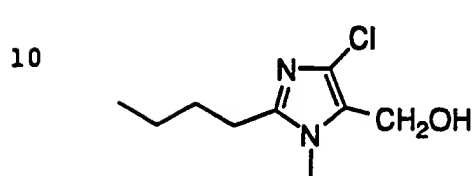
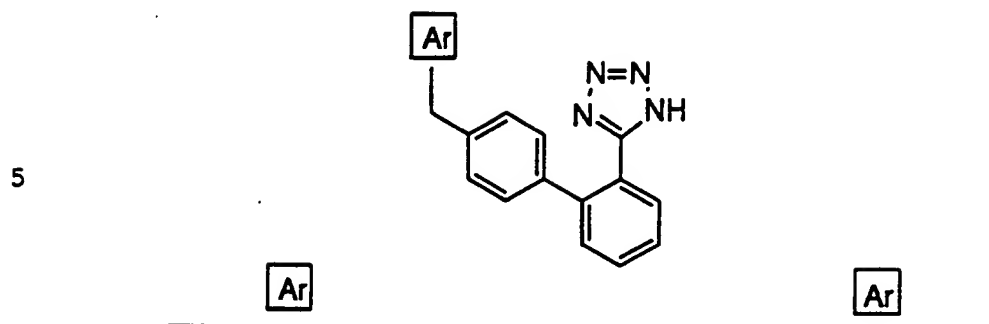
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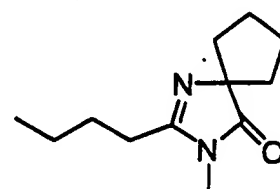


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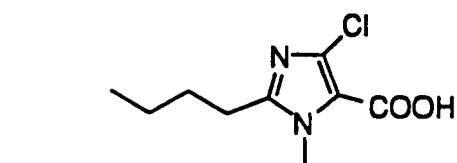
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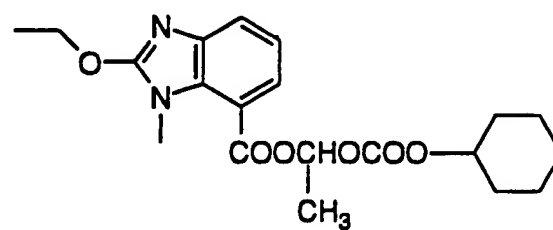
IV (losartan)



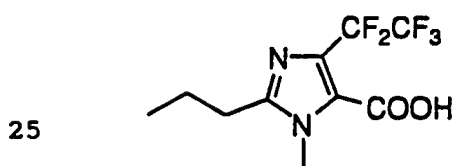
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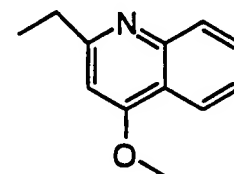
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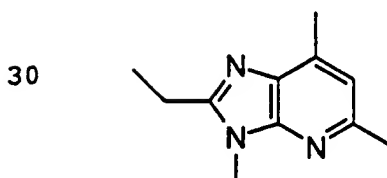
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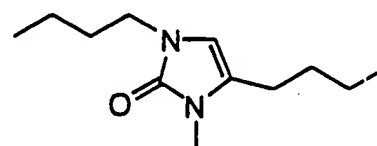
VI



X



VII



XI

- 14 -

and the diuretic is selected from hydrochlorothiazide (HCTZ),
furosemide, altizide, trichlormethazide, triflumethazide, bemetizide,
cyclothiazide, methylclothiazide, azosemide, chlorothiazide, butizide,
bendroflumethazide, cyclopenthiazide, benzclortriazide, polythiazide,
5 hydroflumethazide, benzthiazide, ethiazide, penflutazide,
chlorthialidone, butazolimide, spironolactone, amiloride or triamterene.

8. The method of Claim 7 wherein the A-II antagonist
is losartan.

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9. The formulation of Claim 8 wherein the the diuretic
is hydrochlorothiazide.

10. The method of Claim 9 comprising 2.5, 5.0, 10,
15 12.5, 25, 50 or 100 mg of losartan and 6.25 mg of hydrochlorothiazide.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/10163

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/41, 31/54, 31/34, 31/44, 31/47

US CL :514/381, 223.5, 471, 303, 312

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/381, 223.5, 471, 303, 312

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS + CAS-Iosartan and angiotensin II antagonists and hydrochlorothiazide as antihypertensives or for other heartrelated conditions

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chemical Abstracts, Vol. 117, No. 18, issued 1992, Smithkline Beckman Corp., "Antihypertensive," see Abstract No. 178319h.	1-10
Y, P	Journal of Hypertension, Vol. 1, Supplement 2, issued 1993, Andr��n et al., "Enalapril with Either a 'Very Low' or 'Low' Dose of Hydrochlorothiazide is Equally Effective in Essential Hypertension...", pages 384-386, see the abstract particularly.	1-10

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search

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11 APR 1994

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/10163

(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Journal of Pharmacology and Experimental Therapeutics, Vol. 252, No. 2, issued 1990, Chiu et al., "Nonpeptide Angiotensin II Receptor Antagonists. VII. Cellular and Biochemical Pharmacology of Du P 753 an orally active Antihypertensive Agent", pages 711-718, see entire document.	1-10
Y, P	US, A, 5,164,407 (Greenlee et al.) 17 November 1992, see column 1, lines 16-23 particularly.	1-10
Y	American Journal of Physiology, Vol. 263 (3, part 2), issued 1992, Qing et al., "Chronic Captopril and Losartan (DuP 753) Administration In Rats With High-Output Heart Failure", pages H833-H840, see entire document.	1-10
Y	Goodman and Gilman's, "The Pharmacological Basis of Therapeutics" (6 th Edition), published 1980 by MacMillan (N.Y.), see pages 808-811 and 911, especially pages 810, 811 and 911.	1-10